# EXPERIMENTS TO DETERMINE MODE OF SPREAD OF INFLUENZA*

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The experiments here described were performed on an island in Boston Harbor, on volunteers obtained from the Navy. The work was conducted by a group of officers detailed for that purpose, from the U. S. Navy and the U. S. Public Health Service, consisting of Dr. G. W. McCoy, director of the Hygienic Library, Dr. Joseph Goldberger, Dr. Leake, and Dr. Lake, all on the part of the U. S. Public Health Service; and cooperating with those medical officers, was a group also detailed for this purpose on the part of the U. S. Navy, consisting of Dr. J. J. Keegan, Dr. De Wayne Richey and myself.

The work itself was conducted at Gallops Island, which is the quarantine station of the Port of Boston, and peculiarly well fitted for operations of this kind, serving adequately for the purposes of isolation, observations, and maintenance of the large group of volunteers and personnel necessary to take care of them.

The volunteers were all of the most susceptible age, mostly between 18 and 25, only a few of them around 30 years old; and all were in good physical condition. None of these volunteers, 100 all told in number, had "influenza;" that is, from the most careful histories that we could elicit, they gave no account of a febrile attack of any kind during the winter, except a few who were purposely selected, as having shown a typical attack of influenza, in order to test questions of immunity, and for the purpose of control.

Now, we proceeded rather cautiously at first by administering a pure culture of bacillus of influenza, Pfeiffer's bacillus, in a rather moderate amount, into the nostrils of a few of these volunteers.

These early experiments I will not stop to relate, but I will go at once to what I may call our Experiment 1.

## EXPERIMENTS AT GALLOPS ISLAND

As the preliminary trials proved negative, we became bolder, and selecting nineteen of our volunteers, gave each one of them a very large quantity of a mixture of thirteen different strains of the Pfeiffer bacillus, some of them obtained recently from the lungs at necropsy; others were subcultures of varying age, and each of the thirteen had, of course, a different history. Suspen-

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sions of these organisms were sprayed with an atomizer into the nose and into the eyes, and back into the throat, while the volunteers were breathing in. We used some billions of these organisms, according to our estimated counts, on each one of the volunteers, but none of them took sick.

Then we proceeded to transfer the virus obtained from cases of the disease; that is, we collected the material and mucous secretions of the mouth and nose and throat and bronchi from cases of the disease and transferred this to our volunteers. We always obtained this material in the same way: The patient with fever, in bed, has a large, shallow, traylike arrangement before him or her, and we washed out one nostril with some sterile salt solution, using perhaps 5 c.c., which is allowed to run into this tray; and that nostril is blown vigorously into the tray. This is repeated with the other nostril. The patient then gargles with some of the solution. Next we obtain some bronchial mucus through coughing, and then we swab the mucous surface of each nares and also the mucous membrane of the throat. We place these swabs with the material in a bottle with glass beads, and add all the material obtained in the tray. This is the stuff we transfer to our volunteers. In this particular experiment, in which we used ten volunteers, each of them received a comparatively small quantity of this, about 1 c.c. sprayed into each nostril and into the throat, while inspiring, and on the eye. None of these took sick. Some of the same material was filtered and instilled into other volunteers but produced no results.

Now, I may mention at this point that the donors were all patients with influenza in Boston hospitals; sometimes at the U. S. Naval Hospital at Chelsea, sometimes at the Peter Bent Brigham Hospital, where we had access to suitable cases. We always kept in mind the fact that we have no criterion of influenza; therefore I would like to emphasize the fact that we never took an isolated case of fever, but selected our donors from a distinct focus or outbreak of the disease, sometimes an epidemic in a school with 100 cases, from which we would select four or five typical cases, in order to prevent mistakes in diagnosis of influenza.

Now, thinking that perhaps the failure to reproduce the disease in the experiments that I have described was due to the fact that we obtained the material in the hospitals in Boston, and then took it down the bay to Gallops Island, which sometimes required four hours before our volunteers received the material, and believing that the virus was perhaps very frail, and could not stand this exposure, we planned another experiment, in which we obtained a large amount of material, and by special arrangements, rushed it down to Gallops Island; so that the interval between taking the material from the donors and giving it to our volunteers was only one hour and forty minutes, all told. Each one of these volunteers in this experiment, ten in number, received 6 c.c. of the mixed stuff that I have described. They received it into each nostril; received it in the throat, and on the eye; and when you think that 6 c.c. in all was used, you will understand that some of it was swallowed. None of them took sick.

Then, thinking perhaps it was not only the time that was causing our failures, but also the salt solution —for it is possible that the salt solution might be inimical to the virus—we planned another experiment, to eliminate both the time factor and the salt solution, and all other outside influences. In this experiment we had little cotton swabs on the end of sticks, and we transferred the material directly from nose to nose and from throat to throat, using a West tube for the throat culture, so as to get the material not only from the tonsils, but also from the posterior nasopharynx.

We used nineteen volunteers for this experiment, and it was during the time of the outbreak, when we had a choice of many donors. A few of the donors were in the first day of the disease. Others were in the second or third day of the disease. None of these volunteers who received the material thus directly transferred from cases took sick in any way. When I say none of them took sick in any way, I mean that after receiving the material they were then isolated on Gallops Island. Their temperature was taken three times a day and carefully examined, of course, and under constant medical supervision they were held for one full week before they were released, and perhaps used again for some other experiment. All of the volunteers received at least two, and some of them three "shots" as they expressed it.

Our next experiment consisted in injections of blood. We took five donors, five cases of influenza in the febrile stage, some of them again quite early in the disease. We drew 20 c.c. from the arm vein of each, making a total of 100 c.c., which was mixed and treated with 1 per cent. of sodium citrate. Ten c.c. of the citrated whole blood were injected into each of the ten volunteers. None of them took sick in any way. Then we collected a lot of mucous material from the upper respiratory tract, and filtered it through Mandler filters. While these filters will hold back the bacteria of ordinary size, they will allow "ultramicroscopic" organisms to pass. This filtrate was injected into ten volunteers, each one receiving 3.5 c.c. subcutaneously, and none of these took sick in any way.

The next experiment was designed to imitate the natural way in which influenza spreads, at least the way in which we believe influenza spreads, and I have no doubt it does—by human contact. This experiment consisted in bringing ten of our volunteers from Gallops Island to the U. S. Naval Hospital at Chelsea, into a ward having thirty beds, all filled with influenza.

We had previously selected ten of these patients to be the donors; and now, if you will follow me with one of our volunteers in this ward, and remember that the other nine were at the same time doing the same thing, we shall have a picture of just what was happening in this experiment:

The volunteer was led up to the bedside of the patient; he was introduced. He sat down alongside the bed of the patient. They shook hands, and by instructions, he got as close as he conveniently could, and they talked for five minutes. At the end of the five minutes, the patient breathed out as hard as he could, while the volunteer, muzzle to muzzle (in accordance with his instructions, about 2 inches between the two), received this expired breath, and at the same time was breathing in as the patient breathed out. This they repeated five times, and they did it fairly faithfully in almost all of the instances.

After they had done this for five times, the patient coughed directly into the face of the volunteer, face to face, five different times.

I may say that the volunteers were perfectly splendid about carrying out the technic of these experiments. They did it with a high idealism. They were inspired with the thought that they might help others. They went through the program

in a splendid spirit. After our volunteer had had this sort of contact with the patient, talking and chatting and shaking hands with him for five minutes, and receiving his breath five times, and then his cough five times directly in his face, he moved to the next patient whom we had selected, and repeated this, and so on, until this volunteer had had that sort of contact with ten different cases of influenza, in different stages of the disease, mostly fresh cases, none of them more than three days old.

We will remember that each one of the ten volunteers had that sort of intimate contact with each one of the ten different influenza patients. They were watched carefully for seven days—and none of them took sick in any way.

### EXPERIMENTS AT PORTSMOUTH

At that point, the holidays came, our material was exhausted, and we temporarily suspended our work. In fact, we felt rather surprised and somewhat perplexed, and were not sure as to the next way to turn, and we felt it would be better to take a little breathing spell and a rest.

We started another set of experiments in February that lasted into March, again using fifty volunteers carefully selected from the Deer Island Naval Training Station. These experiments I will not give in detail. They would take too long. They were simply designed and the program was carefully planned, but the way matters turned out became very confusing and perplexing. I will give two instances to explain what I mean by that; and I give them because they are exceedingly instructive and very interesting.

In February and March, the epidemic was on the wane. We had difficulty in finding donors. We were not sure of our diagnosis, having no criterion of influenza. We therefore felt very fortunate when we learned of an outbreak that was taking place at the Portsmouth Naval Prison, only a few hours north of Boston. We at once loaded a couple of automobiles filled with our volunteers, and rushed up to Portsmouth, and there repeated many things that I have described in our first set of experiments. At Portsmouth, out of a large number of cases, we made our selections carefully, taking the typical cases for donors, and transferring the material directly to our volunteers. In about thirty-six hours, half of the number we exposed came down with fever and sore throat, with hemolytic streptococci present, and doubtless as the causal agent. All the clinicians who saw these cases in consultation agreed with us that they were ordinary cases of sore throat.

Another incident: One of our officers, Dr. L., who had been in intimate contact with the disease from early in October, collected material from six healthy men at the Portsmouth Navy Yard who were thought might be in the period of incubation of the disease—we were trying to get material as early as possible, because all the evidence seems to indicate that the infection is transmittable early in the disease. None of the six men came down with influenza, but Dr. L. came down in thirty-six hours, with a clinical attack of influenza, although he had escaped all the rest of the outbreak.

### CONCLUSION

I think we must be very careful not to draw any positive conclusions from negative results of this kind. Many factors must be considered. Our volunteers may not have been susceptible. They may have been immune. They had been exposed as all the rest of the people had been exposed to the disease, although they gave no clinical history of an attack.

Dr. McCoy, who with Dr. Richey, did a similar series of experiments on Goat Island, San Francisco, used volunteers who, so far as known, had not been exposed to the outbreak at all, also had negative results, that is, they were unable to reproduce the disease. Perhaps there are factors, or a factor, in the transmission of influenza that we do not know.

As a matter of fact, we entered the outbreak with a notion that we knew the cause of the disease, and were quite sure we knew how it was transmitted from person to person. Perhaps, if we have learned anything, it is that we are not quite sure what we know about the disease.

[A complete account of the experiment is being published by the U. S. Public Health Service.]